REMARKS

This response and amendment is filed in response to the outstanding Office Action. By the foregoing amendments, the specification has been amended to correct a verb tense and new dependent claims 9-24 have been added that are directed to specific suitable antagonists, doses, and diseases. Support for these new claims can be found throughout the specification, particularly at pages 10 and 17-20. No new matter has been introduced and no amendments have been made in view of the cited art.

Claims 4-6 have been rejected on formal grounds and as being anticipated by or unpatentable over prior art cited by the Examiner. Each of the rejections is addressed in detail below and is believed to be obviated in view of the following remarks.

Rejection of Claims 4-6 Under 35 USC § 112, 1st Paragraph

Claims 4-6 have been rejected under 35 U.S.C. §112, 1st paragraph since, in the Examiner's view, it "does not reasonably provide enablement for all other glycine type NMDA receptor antagonists." The Examiner has asserted that the "specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims." In particular, it is alleged that the specification is not enabling based on the "quantity of experimentation necessary, the amount of direction or guidance provided, presence or absence of working examples and the state of the prior art." No further elaboration is provided as to how or why these factors are considered by the Examiner to be lacking other than the Examiner's assertion that the "specification does not teach that all available and future (to be developed) glycine type NMDA receptor antagonists will cross blood-brain barrier and therefore, will have utility for the intended purpose."

This rejection is respectfully traversed. Applicant submits that one of ordinary skill in the art would be able to practice the claimed invention even with "future" glycine type NMDA receptor antagonists based upon the disclosure in the specification.

Applicant is not required to demonstrate in the specification the effectiveness of all glycine type NMDA receptor antagonists. Applicant notes that most, if not all, known glycine type NMDA receptor antagonists are capable of readily crossing the blood brain barrier. Furthermore, it is known to those skilled in the art that compounds that may not readily cross the blood brain barrier when in an aqueous solution will do so when placed in the proper transport mode, i.e., in other solutions (hydrocarbon solvent, alcohol solvent, and the like) or presented in different forms (crystallized). This would be well within the scope of one of ordinary skill in the art and would not entail undue experimentation.

Applicant also notes that a specification need not contain a working example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without an undue amount of experimentation. *In re Long*, 368 F.2d 892, 151 USPQ 640 (CCPA 1966); *In re Borokowski and Van Venrooy*, 422 F.2d 904, 164 USPQ 642 (CCPA 1970). Here, the specification provides clear direction and guidance to one skilled in the art so that they would be able to readily practice the present invention without an undue amount of experimentation.

Accordingly, Applicant believes that the claimed invention is clearly enabled by the specification and withdrawal of this rejection is requested.

Rejection of Claims 4-6 Under 35 USC § 102(b) in view of Sofia

Claims 4-6 have been rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,055,489 to Sofia. This rejection is respectfully traversed.

Sofia is directed to a method for the prevention and control of hypoxic (oxygen starvation) damage resulting from cerebral ischemic events. Sofia does not discuss neuroprotection, namely the protection of neuronal cells. Rather, Sofia discusses the neuro-protective effect against hypoxic, or oxygen starvation, damage that was investigated in a hippocampal slice model.

Claim 1 of Sofia is "for the prevention and treatment of hypoxic damage following a stroke or other cerebral ischemic events". No differentiation between global and focal ischemia is given, but from the language and use of the work stroke and cerebral ischemic events, one of ordinary skill in the art would believe Sofia limited to focal ischemic events. Evidence in the literature shows that global and focal ischemic events have different mechanisms. This would mean that suitable treatment for focal ischemic events is not likely to be suitable for treatment of global ischemic events.

In contrast, the presently claimed invention is directed to the prevention or reduction of neuronal cell injury from cardiac arrest by the mechanisms of global ischemia and cardiac embolism (claims 4 and 9-13); due to ischemia or embolism in invasive vascular procedures (claims 5 and 14-18); and due to excessive NMDA stimulation in patients with cerebrovascular risk factors (claims 6 and 19-24).

As discussed at page 8 of the present specification, neuroprotection is defined as increasing the tolerance of the glia and neurons of the brain and spinal cord to excessive NMDA activation which results in the prevention of neuronal cell death and promoting functional neuronal recovery, rather than just protecting neurons from ischemia.

As noted in the enclosed paper by DeGraba et al. "Why do neuroprotective drugs work in animals but not humans?", *Neurologic Clinics* 19(2):475-493, (2000), the mechanism of neuronal injury is different in global and focal ischemia. These mechanisms are different from those described in Sofia (and predicted in Leeson et al.). Also, over stimulation of NMDA receptors that leads to neuronal damage or death has a mechanism different from acute excessive elevations of glutamate or hypoxic episodes that occur in stroke. Thus, Sofia (and Leeson et al.) does not disclose neuronal protection (as defined and claimed in the present specification) nor do the models they use correspond to the mechanisms for neuronal injury and death, which the present invention prevents or reduces.

Furthermore, Sofia fails to give specific dosages, duration of treatment or serum levels to attain the results described. Thus, one of ordinary skill in the art, upon reading

Sofia, would not be led to believe that glycine antagonists would be suitable for the prevention or reduction of neuronal cell injury from cardiac arrest by the mechanisms of global ischemia and cardiac embolism; due to ischemia or embolism in invasive vascular procedures; or due to excessive NMDA stimulation in patients with cerebrovascular risk factors.

Accordingly, Sofia simply cannot and does not disclose each and every claim limitation of claims 4-6, namely, the prevention or reduction of neuronal cell injury the prevention or reduction of neuronal cell injury from cardiac arrest by the mechanisms of global ischemia and cardiac embolism (claim 4); due to ischemia or embolism in invasive vascular procedures (claim 5); or due to excessive NMDA stimulation in patients with cerebrovascular risk factors (claim 6). Thus, Sofia cannot anticipate claims 4-6. Withdrawal of this rejection is respectfully requested.

Rejection of Claims 4-6 Under 35 USC § 103 in view of Newell et al.

Claims 4-6 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Newell et al. This rejection is respectfully traversed and reconsideration and withdrawal of the same is requested.

The paper by Newell et al. only confirm the principle that a glycine-site receptor antagonist can provide, in hippocampus slice cultures, some neuroprotection in a specific region (CA1) of the hippocampus. However, in this study, the cultures were deprived of both oxygen and glucose, and thus are not an accurate model for ischemia.

Accordingly, from the disclosure of Newell et al., one of ordinary skill in the art would not be able to practice the claimed invention. Applicant also notes that both in vitro and in vivo animal models, such as the hippocampal slice culture used Newell et al., do not necessarily work in humans. See for example, DeGraba et al. "Why do neuroprotective drugs work in animals but not humans?", *Neurologic Clinics* 19(2):475-493, (2000), which found attempted modifications of mechanisms that appeared to be well tested in animal models have failed in human trials.

Rejection of Claims 4-6 Under 35 USC § 103 in view of Leeson

Claims 4-6 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Leeson. This rejection is respectfully traversed and reconsideration and withdrawal of the same is requested.

This rejection is inapplicable for the reasons given above in the discussion of Sofia. Accordingly reconsideration and withdrawal of the same is respectfully requested.

CONCLUSION

In view of the foregoing amendments and remarks, the present application is now believed to be in condition for allowance. The Examiner is asked to consider this response and amendment and pass the application to allowance. Further and favorable consideration is requested.

Respectfully submitted,

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